

Antibiotic Anaphylaxis

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THE CONTINUED USE OF PENICILLIN and other antibiotics has sensitized large numbers of the population to these drugs. An unfortunate by-product of this circumstance is the occurrence of an increasing number of serious and even fatal anaphylactic reactions following administration of antibiotic agents.

Since Waldbott's²⁰ publication in 1949 of a case in which death followed the injection of penicillin, there has been a growing list of similar reports. Kern¹⁵ collected reports of 18 such cases. Fatalities were recently reported by Altouryan,¹ Higgins and Rothchild,¹³ Thomson,¹⁹ Mayer¹⁷ and Bell.² Welch and co-workers²¹ reported a total of 88 anaphylactoid reactions with 25 deaths collected from a sampling survey of 95 hospitals across the country.

An editorial in the *Journal of Allergy* in 1952 directed attention not only to the importance of unreported fatalities but also to the large number of alarming, near-fatal reactions. Reports of severe cases are included in almost all reports of fatalities.

CASE REPORTS

The following two cases observed by the authors are rather typical of these shock-like reactions.

CASE 1. A 36-year-old housewife was given an intramuscular injection of combined penicillin and streptomycin. These drugs had been administered in the past without difficulty. Less than a minute following the injection the patient said she felt ill and had paresthesias of the face and extremities, substernal pain and nausea. The skin became cold and clammy, the radial pulse was rapid and faint, and respirations were wheezy and labored. Cyanosis developed and the eyelids, lips, face and tongue all became quite swollen. The patient arose from a chair, staggered forward and collapsed unconscious, face down on a bed. Epinephrine was given intramuscularly and benadryl intravenously and the patient regained consciousness. She then vigorously vomited more than a liter of a watery material. Complete recovery took approximately two hours.

Comment: Prompt administration of epinephrine and benadryl was probably lifesaving.

CASE 2. A 66-year-old man who had previously received parenteral antibiotics without any reaction

• *Anaphylactic reactions following the injection of penicillin or other antibiotics have increased greatly during the past several years. These untoward reactions to penicillin were infrequent during the first nine years of penicillin therapy and there can be no doubt that hypersensitivity to these drugs is developing in many people. Therefore promiscuous use of them is to be condemned. It is safer not to use antibiotics parenterally in patients with allergic conditions such as bronchial asthma. The further use of a particular antibiotic should be avoided if the patient has previously shown any hypersensitivity to that drug.*

A questionnaire was answered by more than 1,000 California physicians who reported that over 300 patients had severe anaphylactic reactions from parenteral penicillin and streptomycin. There were seven deaths.

Since the antibiotics should still be used when needed, prevention of anaphylaxis is of fundamental importance. The frequency of these reactions can be greatly reduced by the use of antihistaminic solutions combined with the antibiotics. Treatment of these shock-like reactions demands the prompt administration of epinephrine intramuscularly, antihistaminic solutions intravenously and oxygen.

was given an intramuscular injection of combined penicillin and streptomycin. Almost at once he began to sneeze and perspire freely. He complained of substernal pain. He looked pale and very ill. Respirations became noisy and the pulse was rapid and feeble. The patient became cyanotic, lost consciousness and breathed stertorously. He had tonic and clonic contractions of the entire body and became incontinent. Benadryl and epinephrine were given parenterally and oxygen by mask. The patient regained consciousness within five minutes and was then hospitalized. An electrocardiogram taken while the patient was unconscious showed depression of ST segments across the precordium, as much as 4 mm. in some leads. An electrocardiogram taken several hours later showed only slight depression, 1 mm. or less, of the ST segments in leads V4 to V6.

Comment: The electrocardiographic findings suggesting anoxia or coronary insufficiency are of interest.

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TABLE 1.—Anaphylactic reactions to antibiotics as reported by more than 1,000 physicians answering questionnaire

Antibiotic	Anaphylactic Reactions		Deaths*
	Moderate	Severe	
Penicillin	520	323	7
Streptomycin	49	10	0
Combiotics (penicillin and streptomycin)	0	5	0
Other antibiotics	33	4	0

*Deaths occurred in Berkeley, Centerville, Hayward, Richmond, Sacramento, San Leandro and San Francisco.

To gather data on the incidence of shock-like reaction to antibiotics a brief questionnaire was sent to physicians, chiefly in central California, and more than a thousand replied. The results of the survey are shown in Table 1.

Data on two fatal cases reported in reply to questionnaires follow:

CASE 3. The patient, a 65-year-old pensioner with pulmonary emphysema, congestive heart failure and a purulent bronchitis, had received procaine penicillin G several times in the previous four years, the last injection about nine months previously. Then, when given an intragluteal injection of procaine penicillin G, within approximately 20 seconds the patient collapsed to the floor, had labored noisy respirations, became deeply cyanotic, stopped breathing and was dead in less than a minute after the injection.

Comment: The rapidity of this episode suggests the urgency of starting treatment at once and indicates the necessity of having available emergency medication.

CASE 4. A 60-year-old railroad worker who had received multiple injections of penicillin during the past several years, the most recent approximately six months previously, was given 600,000 units of procaine penicillin G in the arm. Immediately he complained of vertigo and less than a minute later he collapsed to the floor, unconscious. Respirations were shallow and irregular and the pulse was rapid and extremely weak. The blood pressure could not be obtained. The patient died in less than three minutes after the injection. At autopsy, pronounced emphysema and congestion of the lungs with focal areas of atelectasis were noted. The other organs were singularly free of abnormal findings. There was no evidence of pulmonary embolism.

Comment: The paucity of morphologic findings at necropsy is characteristic of anaphylactic death. Death is the result of abnormal physiologic reactions without obvious tissue damage.

Data were obtained on two other fatal cases of the survey. In one a 70-year-old man was given an intramuscular injection of 600,000 units of benzathine penicillin G for bronchopneumonia. Death was sudden. At autopsy pronounced congestion and edema of the lungs and bronchi was observed. The other case, in which autopsy was carried out also, is to be published separately.

DISCUSSION

Since almost 30 tons of penicillin is certified for distribution each month, the astronomical number of injections of the drug is readily apparent. By comparison, the number of anaphylactic reactions which occurs seems small indeed. Nevertheless, a careful and objective appraisal of the problem does not permit a relaxed or comfortable attitude. Kern's¹⁵ analysis, for example, clearly shows that the fatalities following the injection of penicillin have practically all occurred in recent years. This suggests a long, silent period of sensitization to the antibiotics and that now we reap the wild wind of anaphylaxis.

Autopsy findings in two cases have been described by Curphey.⁵ The patients, both asthmatic, had diffuse congestion of the lungs and bronchi. There were dilated, engorged vessels in the bronchial mucosa and considerable mucoid exudate in the trachea and larger bronchi. On microscopic examination, acute congestion of the capillary septa with patchy and irregular dilatation of the alveoli were noted. The bronchioles showed interstitial edema with eosinophils, polynuclears and round cells in the submucosal layer. The remainder of the organs showed pronounced vascular engorgement and interstitial edema. The question arises whether some of these findings were not caused by the bronchial asthma per se. The speed at which a fatal termination occurs suggests not only "physiologic death" but obviously would not permit morphologic tissue changes of any extent except perhaps that caused by edema.

In addition to the fatalities there are a large number of near-fatal and severe anaphylactic reactions. (More than 300 such instances were reported in this survey.) Each of these events is a trying experience for both patient and physician.

All reports in the literature suggest a much higher incidence of these reactions in persons known to have allergic disease such as hay fever or asthma. In addition, the incidence of reactions is definitely greater in persons who previously had any manifestation of sensitivity to the drug, such as urticaria.

According to both the literature and the survey here reported upon, penicillin is the antibiotic that causes anaphylactoid reactions most often—probably owing to the fact that penicillin has been used the longest and in the greatest quantity. Severe shock-like reactions to streptomycin also occur,⁸ but very few such reactions to the tetracyclines are reported. These drugs, of course, have been given by mouth for the most part.

Various forms of penicillin have caused anaphylactoid reactions: crystalline penicillin G, procaine penicillin G, benzathine penicillin G, penethamate and others. It is of interest that these preparations are chemically different compounds. It is believed

after injection they unite with the serum proteins and form antigens¹⁶ giving rise to specific antibodies. Then after immunological conditions are thus created, another injection of the antigen produces an antigen-antibody reaction, setting loose in the blood stream histamine or histamine-like substances which precipitate the alarming shock-like syndrome.⁶ Both experimentally and in humans, antihistaminic agents¹⁰ have been shown to counteract these histamine substances and are therefore indicated in the treatment of the condition.

In the production of anaphylaxis, substances other than histamine may also be responsible.⁴ Campbell and Nicoll³ showed, for example, that a cholinergic substance, possibly a peptone, or a muscle-stimulating compound similar to snake venom or lecithins may share etiologically with the histamines. Undoubtedly, there are multiple anaphylatoxins involved in these explosive reactions. The pathogenetic mechanism is still shrouded in biochemical and immunologic mystery.

PREVENTION OF REACTIONS

An awareness of the danger of anaphylaxis is imperative. Obviously, penicillin and related antibiotics should be used only when there is a definite need or indication for the drug. They should not be given to persons who previously had any of the various allergic manifestations to the drug.^{11, 18} Unless really necessary they should not be used in persons who had or have hay fever, bronchial asthma or allergic conditions. The tetracyclines may be more safely prescribed for those patients. A positive and immediate reaction to skin test with the antibiotic controverts its use; a negative reaction does not rule out the possibility of anaphylaxis. Intravenous injection of penicillin should by all means be avoided.

During the years 1944 to 1951, before the authors used antihistaminic solutions prophylactically, seven severe anaphylactoid reactions were observed in a series of more than 1,000 injections of penicillin, streptomycin or dihydrostreptomycin alone or in combination. Since that time, antihistaminic solutions have been combined with the antibiotics as routine procedure and no severe anaphylactoid reactions have been noted in more than 3,000 injections.

Regarding the antihistaminic solutions, the authors have added one of the following preparations to the diluent before injection: aqueous benadryl (10-20 mg.), pyribenzamine solution (10-20 mg.), histadyl solution (20-40 mg.), or chlortrimeton (4 mg.). Each of these preparations has been equally effective in preventing these shock-like reactions.

There is considerable literature concerning the rationale for the prevention of anaphylactic shock by means of the antihistaminic drugs. Feinberg¹⁰

said: "Numerous reports have appeared which indicate that those antihistamines which effectively antagonize the bronchoconstrictive action of histamine are capable of diminishing the severity of anaphylaxis in the guinea-pig." The antianaphylactic activity of benadryl, pyribenzamine, chlortrimeton, histadyl and other antihistamines have been clearly demonstrated in the laboratory animal.¹⁰

Glazko and Dill¹² reported a high concentration of benadryl in the lungs and spleen of animals to which the drug was given to study its distribution in body tissues. This is of interest since these organs play a vital role in anaphylactic shock. It may be that these antihistamines accumulate at "receptor sites" in competition with histamine.¹²

Corticotropin (ACTH) has been shown to greatly diminish or inhibit anaphylactic shock in guinea pigs if administered one hour before injection of the antigen.¹⁴ Fatal anaphylaxis cannot be prevented by giving corticotropin at the time of the shock reaction. Theoretically, intravenous injection of hydrocortisone should be helpful but this preparation has not been investigated in this connection.

TREATMENT OF THE ACUTE ANAPHYLACTIC REACTION

If the patient can be tided over the first several minutes of the reaction, the chances of survival are good. Hence, immediate, vigorous treatment is imperative. Epinephrine 1:1,000 intramuscularly and antihistaminic solutions intravenously should be administered at once and repeated as necessary. Intravenous injection of aminophyllin has also been recommended. These drugs should be available whenever penicillin is being injected. Oxygen should also be given as soon as possible and preferably under positive pressure to combat pulmonary edema. It is important to prevent obstruction of the airways.

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